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# Milk allergy/intolerance in infancy and cognitive functioning

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# MILK ALLERGY/INTOLERANCE IN INFANCY AND COGNITIVE FUNCTIONING

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**ABSTRACT**

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This study examines the relationship between a history of milk A/I in infancy and intelligence in later childhood. Participants included 74 male and female children ages 3 years to 12 years, referred for psychological evaluation. Backgroun information gathered from the primary caregiver included history of milk A/I in infancy. The Wechsler Scales of Intelligence provided information on the participants level of cognitive functioning. Findings were significant for both ANOVA and chi square analysis, with children in Group One (milk A/I) demonstrating lower IQ scores than children in Group Two (no milk A/I). The findings also suggest a relationship between milk A/I and impairment in verbal skills with a greater disparity between Verbal IQ, as opposed to Performance IQ, for percent of children falling below the cut-off scores for both below average and borderline IQ. The reported history of milk A/I was also shown to be significantly higher among those children referred for psychological evaluation (58%) as opposed to children in the general population (5%).

Discriminant analysis revealed Performance IQ subtests to be useful predictors of history of milk A/I with a 70.8% hit-rate. Verbal IQ subtests were useful predictors of milk A/I with a hit-rate of 72.1%. Two subtests together, Arithmetic and Coding, were also useful predictors with a hit-rate of 73.6%. The current findings also reveal significantly lower IQ scores for males with milk A/I history than for males with no such history. Females with milk A/I show no significant disadvantage compared to females with no milk A/I. Thus, gender is suggested as a determining factor in the relationship between milk A/I and intelligence.

The research supports the conclusion a history of milk A/I in infancy is related to below average intelligence in later childhood. Further supported is the proposed connection between a reported history of milk A/I in infancy and being referred for psychological evaluation in later childhood.

## Acknowledgments

I thank those children--nameless to you who read the following, but unforgettable individuals to I who saw them--without whom this study would not have been possible. I only hope this study can be, at least in some small way, of help to future children, if not to its participants.

A special thank-you to Anthony J. Yost, whose help was consummate in every signification of the term.

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# Chapter 1

## Introduction

It has been estimated educating a special-needs student costs more than twice the amount of educating a regular-education student. A study funded by the United States Department of Education reported schools spent an average of $6,335 during the 1985-86 school year on each special education child, as opposed to an average of $2,780 for other students (Flax, 1989). Approximately 10 percent of all school-age children qualify for special-education services. Black (1997) stated, "Over the past five years, the number of U.S. students receiving federal special education aid has gone from 4.8 million to 5.4 million" (p. 34). Another article reported similar numbers. "During the 1993-94 school year, more than 5 million students with special needs were served at a cost of more than $32 billion--two times that for other students" (Miller, 1997, p. 4).

Even in the best of times, funds are limited. Even when budgets are increased, they still have a limit. It is difficult to develop methods of instruction immediately less costly, even if they are less costly in the long term. While many special-education students might benefit most from one-

on-one instruction, such instruction is extremely costly. If a way of improving the student's ability to perform academically and also of lessening his or her need for special instruction could be found, that would be to the student's advantage, as well as beneficial with regard to the problem of limited funds.

## Nutrition and Learning

Many might not consider the relationship between nutrition and learning relevant to the need for special education. Even so, a "direct relationship between diet and learning" is generally accepted in the sense that children who do not get enough to eat will be impaired in realizing their learning potential (Pertz & Putnam, 1982, abstract, p. 1). The report by Pertz & Putnam, although focusing heavily on the detrimental effects of nutritional deprivation, cited research indicating "protein-poor diets produce children who are less able to learn" (p.1) and who also have lower intelligence quotients and poorer language development.

Hippocrates, the "Father of Medicine," said to those who would listen, "Let thy food be thy medicine and thy medicine be thy food." Maimonides echoed that sentiment when he stated, "No illness which can be treated by diet should be treated by any other means." While this may seem an extremist attitude, the fact is, ignoring the importance of nutrient intake and individual physical reaction to various substances is an equally limited view. A familiar saying is, ”One man's meat is another man's poison.” What one person

can tolerate quite well, may make another person horribly ill. Extremes are more easily noticed. Perhaps less obvious are those more subtle, even if more pervasive, reactions, particularly if those reactions are specific to the individual and not absolute.

Recognizing the importance of diet in connection to behavioral, emotional, and cognitive issues, professionals are more closely examining the various constituents of food items including macronutrients such as fats and proteins, and micronutrients such as vitamins and minerals, in relation to these issues (Lucarelli, et. al., 1995; Renzoni, et. al., 1995; Willats, 1998). Of further relevance is the issue of individual ability to properly handle specific nutrients.

## Proteins, Amino Acids, and Cognitive Functioning

In examining the relationship between specific nutrients, such as proteins and amino acids, and cognitive functioning, it is relevant at this juncture to consider a specific diagnostic category, such as autism. Autism is a disorder generally first diagnosed in childhood, with characteristic delays in social interaction, language development, or symbolic or imaginative play occurring prior to age three. Although manifestations of the disorder vary greatly, the impairment in reciprocal social interaction is generally gross and sustained. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (1994) fourth edition, places the incidence rate

of Autistic Disorder at 2-5 cases per 10,000 individuals. Approximately 75% of children with Autistic Disorder receive a co-diagnosis of mental retardation.

Reichelt, Knivsberg, Lind, and Nodland (1991) reported increased levels of urinary peptides connected with autism. Peptides are chains of amino acids. Proteins are long peptides. This increase in urinary peptides, combined with a significantly increased frequency of elevated IgA (immunoglobulin A) antibodies against specific proteins (casein and gluten), indicate a possible defect of peptidases (enzymatic breakdown of peptides into simpler compounds) in children with autism. Also reported were significant increases ($p<0.005$) in scores of psycholinguistic abilities for children included in the study subsequent to their beginning a diet eliminating foods (cow's milk and/or wheat) containing these specific proteins. The Illinois Test of Psycholinguistic Ability was used as a measure in Reichelt et al.'s study. The Raven's progressive matrices, a test of general intelligence, were also used. Here again, Reichelt et al. reported significant increases ($p<0.01$) in scores subsequent to children beginning the diet eliminating cow's milk and/or wheat. Further noted, despite increased testing time, the children who went off the diet could not complete Raven's matrices which they managed before suspending the diet. Those children only maintaining the milk restrictions had less regression than those who gave up the diet completely. Level

of urinary peptides also decreased for children on the diet, with peptide levels rebounding in those children who quit the diet. For children on the diet, improvements in social relations and decrease in bizarre behavior were the most frequent behavioral changes observed based on consensus of teachers and parents using a behavior rating scale. Teachers also found the children to display improved concentration, and found "more transferable learning to take place" for the children while on the diet eliminating cow's milk and/or wheat (p. 315).

Lucarelli et al. (1995) published similar findings reporting levels of IgA antigen specific antibodies significantly higher in children with autism than in a control group of twenty healthy children. Also reported were higher levels of antigen specific antibodies of the IgG and IgM classes for casein, as well as IgA specific antibodies for ovalbumin (the chief protein occurring in the white of egg). The levels of these antibodies were significantly higher ($p<0.01$ to $p<0.001$) than in the control group. Lucarelli also reported a marked improvement in the behavioral symptoms of subjects with autism after a period of eight weeks on a diet eliminating cow's milk (other foods were eliminated in those cases with a verified positive test to allergen). Significant levels ($p<0.05$) of improvement occurred in behaviors related to autistic isolation, verbal communication, motor disturbances, inappropriate emotional responses, disturbances in feeding behavior, and

disturbances in concentration, perception, and intellectual functioning. In cases where improvement in symptoms was observed a double blind placebo controlled challenge with the food allergen(s) was performed. Participants received a capsule containing either allergen or placebo(sucrose) in randomized order. In three of seven behavioral categories a significant ($p<0.05$) worsening of symptoms occurred following the oral challenge with allergen: 1)motor disturbances, 2)inappropriate emotional responses, and 3)disturbances in concentration, perception and intellectual functioning. Results of this study again underscore the importance of dietary factors, in this instance proteins, in relation to behavior and cognition.

Winsberg, Sverd, Castells, Hurwic, & Perel (1980) discussed findings suggesting an abnormality in monoamine metabolism in some children with autism. Interestingly, monoamines, a class of small-molecule neurotransmitter, are synthesized from a single amino acid. Amino acids are the building blocks of proteins. Winsberg et al. stated in their report high values of glutamic acid displayed by their subjects "may be due to the degradation glutamine to glutamic acid during analysis" (p. 254). Glutamic acid is an amino acid occurring in proteins. Glutamate is a salt or ester of glutamic acid. Glutamate, the main excitatory neurotransmitter in the brain, is an important factor in long term potentiation in N-methyl-D-aspartate(NMDA) receptors. Long term potentiation(LTP), the enduring

facilitation of synaptic transmission that occurs following activation of a synapse, is believed highly relevant to the neural mechanisms of learning and memory. LTP occurs only when the firing of the presynaptic neuron is followed by the firing of the post synaptic neuron. This co-occurrence of firing is considered the critical factor in many types of learning (Pinel, 1997). Furthermore, elevated concentrations of extracellular glutamate are highly toxic to neurons (Purves et al., 1997). Winsberg et al. simply stated the complexity revealed by their findings:

> autism is not a biochemical uniform abnormality, but a broad and heterogeneous diagnostic category. This hypothesis requires considerable further investigation in the area of biogenic amine metabolism in mentally disabled children by differentiating children on the basis of their monoamine, cAMP and aminoacid spinal fluid findings and then, searching for meaningful clinical correlations(p. 255).

Moreno et al. (1992) reported finding levels of glutamate and aspartate (also an amino acid) significantly elevated among individuals with autism. Although the article focused more heavily on amino acid abnormality, they also reported individuals with autism given megadoses of vitamin B6 (pyridoxine) subjectively gained in language abilities and affectivity. Interestingly, gamma aminobutyric acid (GABA), an inhibitory neurotransmitter, is synthesized from glutamate by the enzyme glutamic acid decarboxylase (GAD). The GAD, however, requires a cofactor, pyridoxal phosphate, for activity. Pyridoxal phosphate is derived from vitamin B6

(Purves et al., 1997).

Moreno et al. (1992) were not the only researchers to report on the use of vitamin B6 in treating autism. Vitamin B6 has been reported by several authors to give interesting results in some patients with autism (Barthelemy et al, 1988; Martinueau, Barthelemy, Garreau, & Lelord, 1985; Martinueau, Barthelemy, & Lelord, 1986; see also Wing, 1988). Particularly interesting is the Martineau, Barthelemy, & Lelord (1986) study. Martineau et al. reported improvement of a child with autism in behaviors similar to those behaviors reported improved by Lucarelli et al. (1995). After initiating Vitamin B6/magnesium treatment, the child was rated twice a week using a behavior rating scale (Behavior Summarized Evaluation [BSE]). By Day 60, scores were reduced by 50% or better in the following areas: autistic withdrawal(85%), impairment in communication(50%), bizarre responses to environment(75%), and inappropriate affective response(85%).

Previously, Martineau et al. (1985) reported behavioral improvements observed with the use of B6+magnesium were further associated with significant changes in urinary excretion of the main dopamine metabolite, homovanillic acid(HVA). An inverse relationship was observed between the excretion of HVA and measures of evoked potentials(EP). When HVA excretion decreased, EP amplitude and morphology "normalized." This study involved 60 children with autism and implemented four therapeutic crossed-sequential double-

blind trials: Trial A--B6 plus magnesium/magnesium; Trial B--B6 plus magnesium; Trial C--magnesium; Trial D--Vitamin B6. The changes in behavior, HVA excretion, and EP parameters were not observed when either the B6 or magnesium were administered alone. In Trial A, the lack of a wash out period did not allow for determining the respective effects of each treatment, and the delayed effects of B6 and of magnesium each contaminated the effects of the other.

Barthelemy et al. (1988), evaluated the therapeutic effects of vitamin B6 and magnesium treatment in 91 children with autism. According to the clinical response, four subgroups were clearly discernible: 12 children were highly responsive (14%), 30 children improved (33%), 39 children were unchanged (42%), and 10 children became worse (11%). When compared with the unchanged children, analysis showed children sensitive to treatment had higher urinary HVA levels pre-treatment. These high urinary levels decreased after two weeks treatment. Behavior changes as rated on the Behaviour Summarized Evaluation (BSE), were significant in areas relating to autistic withdrawal, verbal and non-verbal communication, and bizarre responses to the environment. Specific behavior changes included social interaction ($p<0.001$), effort to communicate ($p<0.001$), resistance to change and frustration ($p<0.001$), and stereotyped sensori-motor activity ($p<0.001$). And like Martineau et al. (1985), Barthelemy et al. reported a tendency toward normalization of cortical response as shown by evoked potentials.

The reported efficacy of B6+magnesium treatment in children with autism is particularly interesting when one considers that B6 has an important role in the breakdown of peptides. Again, peptides are chains of amino acids; proteins are long peptides. In order for the body to absorb proteins, the proteins must first be broken down into amino acids. Although the digestion of amino acids is slow, the absorption occurs rapidly. This absorption requires B6. In fact, B6 is a precursor to over 60 enzyme reactions and is necessary for the proper metabolization of all the amino acids (Philpott & Kalita, 1987). For example, B6 plays a major role in tryptophan to niacin conversion. Niacin also has as a major function in metabolizing proteins, carbohydrates, and fats. Magnesium, necessary for neural transmission, also activates many enzymes (Quillman, 1994). Further relevant to consider, the "normal activity of all life depends on unhampered action of enzymes..." and the "enzyme equipment of any cell is a major expression of its genetic constitution (DNA structure)" (Frobisher, Hindsill, Crabtree, & Goodheart, 1974, p. 96).

Furthermore, it is also known that large doses of B6 will elevate serotonin levels (Coleman, 1973; Bhagavan, Coleman, & Coursin, 1975 [as cited in Rimland, Callaway, & Dreyfus; 1978]). Both vitamin B6 and the mineral magnesium are active in the metabolism of dopamine (Barbeau, et al., 1973; Coleman, et al., 1979; Durlach, 1976; Yahr, Duvoisin, Cote, and Cohen, 1972 [as cited in Barthelemy et al.,

1981]). Dopamine and serotonin, two types of monoamine neurotransmitters, are each constituted of amino acids commonly found in proteins (Pinel, 1997; Stedman, 1995). Dopamine has been indicated in several important functions such as movement, attention, learning, and addictions. Serotonin is a factor in mood, eating, sleep, and arousal. Drugs interfering with serotonin function are known to increase dreaming or even to cause hallucinations (Carlson, 1992). Abnormal levels of neurotransmitters or their metabolites have been implicated in many neurobiological disorders. Not surprisingly, some authors have suggested involvement of one or both of these two systems, serotonergic and dopaminergic, in autism (Heeley and Roberts, 1965; Kohler, J., 1988; Rolf, Harman, Grotemeyer, and Kehrer, 1993; Shattock and Lowdon, 1991). The findings discussed in this section on Proteins, Amino Acids, and Cognitive Functioning are summarized in a later table.

Other Dietary Factors and Cognitive Functioning

Amino acids have not been the sole focus of researchers studying the relation between diet and cognitive functioning. Willats, Forsyth, DiModungo, Varma, and Colvin (1998) reported findings suggesting long-chain polyunsaturated fatty acids (LCPUFA), important for normal visual and brain development, are also related to abilities of means-end problem solving. These researchers reported findings suggesting the importance of LCPUFA for the "development of childhood intelligence" (p. 688).

LCPUFA, present in human milk, until recently have been absent from artificial formulas. Willats et al., in looking at the clinical significance of LCPUFA deficiency, randomly assigned 44 infants to either a formula supplemented with LCPUFA or not so supplemented. Cognitive functioning was assessed at ten months of age using a means-end problem solving test. Infants who received the LCPUFA-supplemented formula had significantly ($p<0.021$) higher scores of intentional solutions than did the second group. The researchers interpreted these findings as being suggestive of benefits that may persist beyond the period of supplementation because higher problem solving scores in infancy are related to higher childhood IQ scores.

Similarly, Kaleita, Kinsbourne, and Menkes (1991), in examining children who demonstrated a failure-to-thrive pattern in infancy attributable to chloride-deficient Neo-Mull-Soy formula, found the children to have distinctive cognitive impairments four to nine years later. Although global intellectual functioning was within the normal range for these children, they displayed problems including "a language disorder primarily involving articulation, word finding and naming; visual-motor and fine-motor difficulties; and attention deficit disorder, often featuring repetitive behaviours, withdrawal and perseveration" (p. 1118). Thirteen children exposed to the grossly chloride-deficient formula were examined. All of the children had histories of normal gestation, delivery, and

neonatal period. The Wechsler Preschool and Primary Scales of Intelligence, the Stanford-Binet Intelligence Scale, and the Wechsler Intelligence Scale for Children-Revised were used to assess general intelligence. The various parameters of language were tested using: Peabody Picture Vocabulary Test(receptive vocabulary), Token Test for Children (auditory comprehension), Boston Naming Test (naming), Rapid Automatized Naming Test (verbal fluency: rapid naming), Word Fluency Tests (verbal fluency: name generating), Sentence Repetition Test (sentence memory). The Beery Developmental Test of Visuomotor Integration was also used to assess level of functioning. All thirteen children met the diagnostic criteria for attention deficit hyperactivity disorder. And although each child was easily distracted by internal or external stimuli, many children (7 of the 13) displayed a more unusual defect in attention with difficulties of "overfocus" of attention. The majority of these children (11 of 13) were cognizant of their difficulties, "and both clinical observations and parent reports indicate low self-esteem, as demonstrated by self-deprecating expressions and reluctance to speak during conversations" (p. 633).

In keeping with the foregoing, aflatoxins (toxic metabolites of some strains of Aspergillus flavus, Aspergillus parasitus, Aspergillus oryzae as well as some Penicillium strains) have been linked to mental retardation. In a region of southern Georgia known for poor school performance, the mothers of children with mental retardation

had diets that, while not differing in terms of *critical* nutrients, differed from average in terms of foods. Researchers (Castor, Burton, Irvin, and Tanner, 1986) reported that consuming large amounts of corn, rice, peanuts, and milk (foods potentially high in aflatoxins) was significantly related to mental retardation. Data gathered from another Georgia county having low levels of dietary aflatoxins displayed "no such relationship" (p. 291). Diet histories were gathered from 249 mothers in two counties, one county having low levels of dietary aflatoxins, the other county having high levels of dietary aflatoxins. Castor et al. (1986), reported significant differences between the diet of mothers with children in the group with retardation and the diet of mothers with children in the high ($p<0.0001$) and the gifted ($p<0.001$) groups. Also, as the total servings of corn, rice, and peanuts increased, and the milk consumption increased, "the IQ of the average child decreased" (p. 293). The probability of encountering a food item with high concentrations of aflatoxins would also increase with the increased ingestion of these food items. In this instance the dietary culprit would appear to have been a fungal contaminant, or perhaps more precisely, its toxic metabolite. Aflatoxins appear to "inhibit enzymes involved in the synthesis of DNA and hence in the synthesis of RNA and proteins" (Frobisher, Hindsill, Crabtree, & Goodheart, 1974, p. 166). The findings discussed in this section on Other Dietary Factors and Cognitive Functioning

are summarized in a later table.

Cow's Milk versus Breast Milk and Cognitive Functioning

Some researchers (Florey, Leach, & Blackhall, 1995; Lucas, Morley, Cole, Lister & Leeson-Payne, 1992; Morley, Cole, Powell & Lucas, 1988; Morley & Lucas, 1994) have considered the possibility of difference in nutrients or other biological factors in cow's milk versus human breast milk when comparing children's intelligence levels among those who have or have not been breast fed. In investigating developmental status at 18 months among 771 low birthweight infants, Morley et al. (1988) reported an 8 point advantage in mean Bayley mental developmental index for babies whose mothers chose to provide breast milk as compared to those infants whose mothers chose not to do so. Data collected on demographic (family structure, social class, and mother's education) and perinatal (pregnancy, labor, delivery, and neonatal period) factors were analyzed for association with the mental developmental index and IQ equivalent, using multiple regression with the mental developmental index and IQ equivalent as dependent variables. After adjusting for associated factors, a 4.3 point advantage remained ($p<0.005$). One may generally argue the Bayley Scales, like other evaluative instruments designed for use with infants, should be used principally in the assessment of current developmental status rather than as a predictor of later ability since the Bayley Scales do not always correlate well with IQ scores in later childhood (Anastasi, 1988). Even so,

data gathered when these same children were age 7 1/2 to 8 years of age demonstrated an 8.3 point advantage in IQ using the WISC-R, even after adjustment for differences between groups in mothers' education and social class (Lucas et al., 1992). The researchers stated, "Although these results could be explained by differences between groups in parenting skills or genetic potential (even after adjustment for social and educational factors), our data point to a beneficial effect of human milk on neurodevelopment" (p. 613). Similarly, Morley & Lucas (1994, abstract) reported findings suggesting, "human milk may contain factors which promote brain growth or development . . . later in childhood" (p. 123).

Although reporting "further evidence of a robust statistical association" (p. S21) between breast feeding and child intelligence, Florey et al. (1995) appeared cautious in presenting the importance of their findings as they again brought to the reader's attention the need to consider potentially confounding variables such as method of feeding, social environment, and parental intelligence. They called for studies "designed to disentangle the relation" between such variables. One factor in such caution and subsequent calls for disentangling is some studies have not shown such robust statistical associations. Even so, Florey et al. admitted although the relationship between breast feeding and intelligence has been reported in the medical press for at least 60 years, two observations are apparent. (1)"Breast

feeding is related in a statistical sense to children's mental development" (p. S25) (2)"No author has been willing to be committed to the conclusion that bottle feeding is likely a disadvantage to the child's intellectual development" (p. S25).

More recently, however, after controlling for environmental factors and maternal intelligence, Johnson, Swank, Howie, Baldwin, & Owen (1996) reported findings that again associate breast feeding with children's intelligence. In addition to a 7.3 point advantage on measures of receptive vocabulary knowledge, they reported a 4.6 point higher mean IQ score associated with breast feeding. Oski (1993), as stated in *Current Opinion in Pediatrics* believed "it is becoming increasingly apparent that infants who receive human milk develop differently from infants who receive infant formulas" (p. 385). Even so, Johnson et al.'s findings are tempered by the observation that, while a difference of 4.6 points in mean IQ on the Stanford Binet is twice the standard error of measurement for that instrument, 2.8 points (composite score), it is much less than the Stanford Binet's Standard Deviation of 16 points. The 7.3 point advantage on measures of receptive vocabulary knowledge reported by Johnson et al. may be the more notable indicator.

Coupling a formula related disadvantage in cognitive development with the heightened negative reactions in children who demonstrate allergy or intolerance to formula,

might such milk allergic/intolerant children display an even greater degree of impact on cognitive functioning? Host (1994), in considering some clinical, epidemiological, and immunological aspects of cow's milk allergy/intolerance in infancy, places the incidence rate of such at about 2-5% in developed countries. Those reactions immunologically mediated, mainly immediate IgE-mediated reactions, are described as cow's milk protein allergy (CMPA), while non immunological mediated reactions against CMP are described as cow's milk protein intolerance (CMPI). Host further reminded, "It is not possible to differentiate between CMPA and CMPI solely on clinical symptoms" and "No single laboratory test is diagnostic of CMPA/CMPI" (p. 1). Host reported that in his Danish investigation a cohort of 1,749 newborns followed during the first year of life evidenced a 2.2% incidence rate of CMPA/CMPI. He cited additional research (e.g. Bock, 1987; Jacobsson & Lindberg, 1979; Schrander et al., 1993) providing similar numbers. In addition to epidemiology, Host's report provides useful information relating to clinical features, symptomology, immunology, diagnosis, and treatment of CMPA/CMPI. Interestingly, many children who have demonstrated problems with formulas containing cow's milk are returned to diets containing cow's milk generally at the age at which formula use is discontinued. A common perception is these children have "outgrown" the allergy/intolerance.

In considering dietary impact on cognitive functioning,

it is further relevant to consider subsequent increases in the need for instruction beyond that provided in a regular-education setting for those children who may be affected either cognitively or behaviorally by individual diet. If dietary factors are indeed impacting the cognitive functioning of some children it would be remiss to ignore the import of dietary factors in relation to educational concerns, either of an individual nature or in terms of broader scope. As costs, both in terms of education dollars and in terms of lost human potential, continue to climb, the issue becomes one of not only fiscal practicality, but also an issue of responsibility to the individual child. As discussed at the beginning of this proposal, if a way of improving the student's ability to perform academically and also of lessening his or her need for special instruction could be found, such improved performance would be valuable in the management of limited funds. More importantly, improving the student's ability to perform academically would be beneficial to the individual child.

## Summary of Research Findings

Pertz and Putnam's (1982) stated connection between proteins and learning was less than specific, although they declared a "direct" relationship between the two. Reichelt et al. (1991) specified proteins casein and gluten as being related to language development, intelligence, and autistic behavior in children with autism. Lucarelli (1995) published findings similar to those of Reichelt et al., regarding not

only casein and gluten, but also ovalbumin, the main protein found in egg white. Winsberg et al. (1980) previously discussed findings suggesting possible abnormalities in monoamine metabolism in children with autism. Proteins are long peptides; peptides are chains of amino acids. Several authors have reported significant improvements in children with autism after treatment with micronutrients Vitamin B6+magnesium (Barthelemy et al, 1988; Martinueau, Barthelemy, Garreau, & Lelord, 1985; Martinueau, Barthelemy, & Lelord, 1986; see also Wing, 1988). Interestingly, these same micronutrients are known to play an important role in the metabolization (breakdown) of amino acids.

In examining the role of other dietary factors in relation to cognitive functioning, Willats et al. (1998) reported findings suggesting long-chain polyunsaturated fatty acids are related to means-end problem solving and of further relevance to the development of childhood intelligence. Children were noted by Kaleita et al. (1991) to have distinctive cognitive impairments in later childhood after having received formulas deficient in chloride. Toxic metabolites such as aflatoxins have been linked to mental retardation in an area of Georgia known for poor school performance (Castor et al. 1986).

Several researchers have reported findings linking breast milk, as opposed to formula, to higher intelligence levels (Florey, Leach, & Blackhall, 1995; Lucas, Morley, Cole, Lister & Leeson-Payne, 1992; Morley, Cole, Powell &

Lucas, 1988; Morley & Lucas, 1994). Morley et al. (1988) reported and 8 point advantage in mean Bayley mental developmental index for infants on breast milk as compared to those infants fed formula. After adjusting for demographic and perinatal factors, a 4.3 point advantage remained. When the same children were 7 1/2 to 8 years of age, an 8.3 point advantage in IQ for the breast fed children was demonstrated even after adjustment for differences between groups in mother's education and social class (Lucas et al., 1992). More recently, researchers have added to the findings in support of stated beneficial effects on cognitive functioning of breast milk as opposed to formula (Florey et al., 1995; Johnson et al., 1996; Morley et al., 1994). The above information is summarized in Table 1.

Though one might expect a more extensive literature relating specific dietary factors to cognitive functioning, literature searches using Biology Digest, Medline, and psychological abstracts did not reveal other research of relevance. When asked about the apparent dearth of relevant literature, R. Wiggins (personal communication, Sept. 10, 1999) commented that there is as an actual paucity of literature available relating specific dietary factors to cognitive functioning.

Table 1

Dietary Factors

| Author | Dietary Factor | Linked to | N |
|---|---|---|---|
| Lucarelli et al. (1995) | protein | IQ, language development, and autistic behavior | 56 |
| Reichelt et al. (1991) | amino acids | IQ, language development, and autistic behavior | 44 |
| Winsberg et al. (1980) | amino acids | autism | 8 |
| Moreno et al. (1992) | amino acids | autism and language development | 60 |
| Moreno et al. (1992) | B6 | language development | 60 |
| Martineau et al. (1986) | B6+mg | language development, and autistic behavior | 1 |

(*table continues*)

Table 1 (*continued*)

Dietary Factors

| Author | Dietary Factor | Linked to | N |
|---|---|---|---|
| Martineau et al. (1985) | B6+mg | autism | 60 |
| Barthelemy et al. (1988) | B6+mg | autistic behavior | 91 |
| Willats et al. (1998) | LCPUFA | cognitive functioning | 44 |
| Kaleita et al. (1991) | chloride | IQ, language development, attention, and motor development | 13 |
| Castor et al. (1986) | aflatoxins | IQ | 249 |
| Morley et al. (1988) | human vs. cow's milk | IQ | 771 |
| Florey et al. | human vs. cow's | IQ | 592 |

| | | | |
|---|---|---|---|
| (1995) | milk | | |

(*table continues*)

Table 1 (*continued*)

Dietary Factors

| Author | Dietary Factor | Linked to | N |
|---|---|---|---|
| Johnson et al. (1996) | human vs. cow's milk | IQ | 204 |

Research Questions

In relation to the foregoing, it is proposed a reported history of problems with cow's milk in infancy may be related to increased difficulties, such as below average cognitive functioning, for some individuals. The current study examines three dimensions of this question. (1) Do children referred for psychological evaluation have an increased tendency to display below average cognitive functioning on objective measures of intelligence when having a reported history of cow's milk allergy/intolerance in comparison to children referred for evaluation who have no such reported history? (2) Do children referred for psychological evaluation report an increased incidence of cow's milk allergy/intolerance as compared to the general population (2-5%, Host, 1994)? The children may be displaying no problems in terms of global intellectual functioning (i.e. Full Scale IQ), but may display difficulties in more specific areas of functioning (e.g. attention, language skills, perceptual organization) resulting in their having been referred for evaluation? (3) Which of the Wechsler Intelligence Scale subtests yield the strongest relationships to a reported history of milk allergy/intolerance in infancy?

# Chapter 2

## Method

### Participants

Participants included male and female children, age 3 years to 12 years, referred to a private-practice office for psychological evaluation. Pediatricians, family physicians, Department of Health and Human Services workers, as well as parents served as referral sources. The study included 74 children. Only children accompanied to the evaluation by an adult familiar with the child's developmental history (e.g., parent) were included in this study. Participants were from the northern half of West Virginia. Approval for the research was obtained from the Institutional Review Board for the Protection of Human Subjects.

### Instruments

The Wechsler Preschool and Primary Scale of Intelligence-Revised (ages 3 years to 5 years, 11 months) and the Wechsler Intelligence Scale for Children-III (ages 6 years to 17 years, 11 months) are objective tests of intelligence. Both scales provide three separate IQ scores: Verbal, Performance, and Full Scale. The Wechsler Scales have demonstrated excellent reliability in assessing intelligence in children, with average internal consistency reliability coefficients for Full Scale IQ on both forms

being 0.96. Internal consistency reliability coefficients for the Performance Scale IQ and the Verbal Scale IQ of both forms ranges from 0.90 to 0.94 (Sattler, 1992).

Design and Procedure

Data gathered over an 18 month period in a private-practice office providing complete psychological services, including an evaluation and testing program, were analyzed. Specifically, those psychological evaluations performed on children age 3 years through 12 years, who were accompanied to the evaluation by an adult familiar with the child's developmental history, were used to provide data on level of intellectual functioning as well as history of milk allergy/intolerance. The participant's primary caregiver (in greater than 90% of cases the participant's mother) was interviewed in order to obtain background information relevant to the participant, including but not limited to, history of allergy/intolerance. The following questions were asked regarding history of allergy/intolerance: (1)Did the child experience difficulties with formula in infancy requiring a physician recommended switch in formulas? When a response stated only that a child was breast fed, the care-giver was again queried. Did the child experience difficulties during infancy, whether breast-fed or not, requiring a physician recommended switch in formulas? (2)Has the child returned to a diet containing whole cow's milk products?

Certainly a physician's report might have been

preferable regarding the history of allergy/intolerance, but such a report was neither obtainable in most instances, nor was it a feasible pursuit logistically. It would appear, in the case of such an obtained history from a primary caregiver, the tendency would be to err on the conservative side. That is, it would appear more likely a parent or caregiver would forget a history of milk related problems in infancy rather than remember such a history falsely. Thus, if anything, the tendency would seem to be to err on the side of caution in rejecting a null hypothesis.

Referral sources were family physicians, pediatricians, parents, teachers, and mental health professionals. Participants were typically referred for psychological evaluation after exhibiting difficulties in one or more areas of functioning (e.g. social, emotional, and intellectual).

The Wechsler Scales were administered along with other pertinent tests. Only the scores demonstrated by the Wechsler Scales were used for the purpose of this study. The Wechsler scales consist of subtests divided into two major divisions yielding a verbal IQ and a performance IQ. Subtests contributing to the WISC-III Verbal IQ score are: Information, Comprehension, Arithmetic, Similarities, and Vocabulary. The performance section of the WISC-III consists of the following subtests: Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly. Subtests contributing to the WPPSI-R Verbal IQ score are the

same subtests as in the WISC-III. The performance section of the WPPSI-R is somewhat different from the WISC-II in that it consists of the following subtests: Picture Completion, Mazes, Geometric Design, Block Design, and Object Assembly.

For the purpose of analysis the upper limit of below average intelligence (89 points Wechsler) and borderline intelligence (79 points Wechsler) were used as cut-off points. Though the texts (Sattler, 1992; Wechsler, 1991) give the range of scores for classification of intellectual functioning, they provide little, if any, information regarding typical levels of accompanying adaptive behaviors for the below average range of functioning and for the borderline range of functioning. The American Psychiatric Association (1994) tells us that Borderline Intellectual Functioning, as a diagnostic category, can be extended as high as an IQ score of 84, presumably when the level of adaptive functioning is substantially impaired. The DSM-IV (1994) tells more regarding the various levels (mild, moderate, severe, and profound) of mental retardation. Perhaps this is due to the tremendous variability in adaptive behavior evidenced across the classifications of below average and borderline.

# Chapter 3

## Results

In relation to the hypothesis a reported history of problems with cow's milk in infancy may be related to increased difficulties, such as below average cognitive functioning, statistical analyses were performed to examine three dimensions of this question. (1) Do children referred for psychological evaluation have an increased tendency to display below average cognitive functioning on objective measures of intelligence when having a reported history of cow's milk allergy/intolerance in comparison to children referred for evaluation who have no such reported history? (2) Do children referred for psychological evaluation report an increased incidence of cow's milk allergy/intolerance as compared to the general population (2-5%, Host, 1994)? (3) Which Wechsler Intelligence Scale subtests yield the strongest relationships to a reported history of milk allergy/intolerance in infancy?

For analysis, participants were differentiated into two groups. Group One consisted of participants with a reported history of milk allergy/intolerance in infancy (n = 43). Group Two consisted of participants with no such reported history (n = 31).

### Research Question 1

Nonparametric tests. In Analysis One, participants in

both Group One and Group Two were further differentiated by IQ scores ≤ 89 (below average), as opposed to those participants with IQ scores ≥ 90 (average and above), thus providing four separate categories of participants. This was done for each of the three IQ scales: Full, Performance, and Verbal. In Analysis Two, participants in both Group One and Group Two were differentiated by IQ scores ≤ 79 (at or below borderline intellectual functioning), as opposed to those participants with IQ scores ≥ 80 (low average and above), thus providing four separate categories of participants. This was done for each of the three IQ scales: Full, Performance, and Verbal. The cut-off points selected for both Analysis One and Analysis Two were based upon those cut-off scores designated in the literature (Sattler, 1992; Wechsler, 1991) regarding the given level of intellectual functioning (e.g., below average and/or borderline). Below average (89 points or lower), as a category of intellectual functioning, typically corresponds with an IQ score of approximately one full standard deviation (15 points Wechsler Scale) below the mean (100 points Wechsler Scale). Borderline (79 points or lower), as a category of intellectual functioning, typically corresponds with an IQ score of approximately two full standard deviations (30 points Wechsler Scale) below the mean (100 points Wechsler Scale). On page 32 of the WISC-III manual (1991), Table 2.8 indicates an IQ score of 89 points as the upper limit of intellectual functioning in the below average range. The

same table indicates an IQ score of 79 points as the upper limit of intellectual functioning in the borderline range.

For each scale, a between groups design was used, and a chi square test for significance of difference was performed. The number of participants in each category was tallied and compared to arrive at an expected, as well as an observed, frequency for each category. Frequencies were in turn used to arrive at a computed chi square in order to discern any statistically significant difference at the 0.05 level. In Analysis One, with an IQ score cut-off criterion of $\leq$ 89 points, varying levels of significance were found across these three scales. Table 2 presents these findings.

On the Full Scale IQ score, 42 of 43 participants (98%) in Group One demonstrated IQ scores $\leq$ 89, and 25 of 31 participants (81%) in Group Two demonstrated IQ scores $\leq$ 89. This resulted in a significant finding (Table 2) indicating a greater proportion of Group One (milk allergy/intolerance) participants to be below average on Full Scale IQ scores than were Group Two (no milk allergy/intolerance) participants. With the Performance IQ score, 40 of 43 participants (93%) in Group One demonstrated IQ scores $\leq$ 89, and 24 of 31 participants (77%) in Group Two demonstrated IQ scores $\leq$ 89 indicating a tendency toward a difference between groups on the Performance measure. This resulted in a trend toward significance as may be seen in Table 2. Verbal IQ scores displayed the most disparity of the three scales, with 40 of 43 participants (93%) in Group One

demonstrating IQ scores ≤ 89, and 21 of 31 participants (68%) in Group Two demonstrating IQ scores ≤ 89. The

Table 2
Chi Square Tests--Below Average IQ

| Scale | *X*-square | p< |
|---|---|---|
| Full | 6.11 | 0.025 |
| Performance | 3.75 | 0.06 |
| Verbal | 7.93 | 0.005 |

Note. Cut-off score criterion was IQ ≤ 89 versus ≥ 90.

$n_1$ = 43. $n_2$ = 31.

df = 1.

findings were significant (Table 2) with a greater proportion of Group One participants below average on Verbal IQ scores.

In Analysis Two, with an IQ score cut-off criterion of ≤ 79, varying levels of significance again were found across the three IQ scales: Full, Performance, and Verbal. Differences were significant for each of the three scales with a greater proportion of participants in Group One than in Group Two falling at or below borderline intellectual functioning for each scale. Table 3 presents these findings. On the Full Scale IQ score, 38 of 43 participants (88%) in Group One demonstrated IQ scores ≤ 79, and 18 of 31 participants (58%) in Group Two demonstrated IQ scores ≤ 79. This resulted in a significant finding (Table 3) with a greater proportion of Group One participants below average on Full Scale IQ scores than were Group Two (no milk allergy/intolerance) participants. With the Performance IQ score, 35 of 43 participants (81%) in Group One demonstrated IQ scores ≤ 79, and 18 of 31 participants (58%) in Group Two demonstrated IQ scores ≤ 79. This resulted in a significant finding (Table 3) with a greater proportion of Group One (milk allergy/intolerance) participants below average on Performance Scale IQ scores than were Group Two (no milk allergy/intolerance) participants. Verbal IQ scores reveal

37 of 43 participants (86%) in Group One demonstrating IQ scores ≤ 79, and 17 of 31 participants (55%) in Group Two demonstrating IQ scores ≤ 79. The findings were significant

Table 3

Chi Square Tests--Borderline IQ

| Scale | *X*-square | p< |
|---|---|---|
| Full | 8.99 | 0.005 |
| Performance | 4.81 | 0.05 |
| Verbal | 8.90 | 0.005 |

Note. Cut-off score criterion was IQ ≤ 79 versus ≥ 80.

df = 1.

$n_1$ = 43. $n_2$ = 31.

(Table 3) with a greater proportion of Group One participants below average on Verbal IQ Scores.

Parametric tests. In order to test the effects of group (allergy/intolerance versus no allergy/intolerance) and gender as independent variables when IQ scores were continuous dependent variables, three analyses of variance were computed. Thus, each analysis of variance was a two by two format with the IQ score (Full Scale, Performance, or Verbal) as the dependent variable.

The first analysis of variance (group by gender) on Full Scale IQ indicated a significant main effect for group, $F$,(1,70) = 7.33, $p$<0.01. The gender main effect was non-significant, $F$,(1,70) = 0.10, $p$>0.05. The interaction of group by gender yielded $F$,(1,70) = 2.63, $p$=0.10. This strong trend in the interaction was interpreted using the Tukey test for multiple comparisons. This interpretation of the interaction indicated no significant difference between males and females for either the allergy/intolerance group or the no-allergy/intolerance group. Similarly, females in the no-allergy/intolerance group did not differ significantly from females in the allergy/intolerance group. Males, however, differed significantly in the two groups. Males in the no-allergy/intolerance group (FSIQ = 75.59) scored significantly higher ($p$<0.01) than males in the allergy/intolerance group (FSIQ = 62.62). The means for this

analysis of variance for Full Scale IQ (main effects and interaction) are presented in Table 4.

Table 4
FSIQ--Means and Standard Deviations for the ANOVA Group by Gender

| | | Females | Males | Group Main Effect |
|---|---|---|---|---|
| A/I (Group1) | M (SD) | 68.64 (11.06) | 62.62 (13.97) | 64.58 (13.27) |
| | n | 14 | 29 | 43 |
| No-A/I (Group2) | M (SD) | 69.56 (17.94) | 75.59 (15.62) | 73.84 (16.26) |
| | n | 9 | 22 | 31 |
| Gender Main Effect | M (SD) | 69.00 (13.77) | 68.22 (15.93) | |
| | n | 23 | 51 | |

Note. A/I = Allergy/Intolerance.

df = 1,70.

The second analysis of variance (group by gender), Performance IQ, indicated a significant main effect for group, $F$,(1,70) = 6.42, $p$<0.01. The gender main effect was non-significant, $F$,(1,70) = 0.09, $p$>0.05. The interaction of group by gender yielded $F$,(1,70) = 2.30, $p$=0.13. This strong trend in the interaction was interpreted using the Tukey test for multiple comparisons. This interpretation of the interaction was similar to that seen in the multiple comparison of the first analysis of variance and indicated no significant difference between males and females for either the allergy/intolerance group or the no-allergy/intolerance group. Again, females in the no-allergy/intolerance group did not differ significantly from females in the allergy/intolerance group. Males did differ significantly in the two groups. Males in the no-allergy/intolerance group (PIQ = 78.55) scored significantly higher ($p$<0.01) than males in the allergy/intolerance group (PIQ = 65.83). The means for this analysis of variance for Performance IQ (main effects and interaction) are presented in Table 5.

The third analysis of variance (group by gender), Verbal IQ, indicated a significant main effect for group, $F$,(1,70) = 5.69, $p$<0.01. The gender main effect was non-significant, $F$,(1,70) = 0.27, $p$>0.05. The interaction of group by gender yielded $F$,(1,70) = 1.91, $p$=0.17. This trend

in the interaction was interpreted using the Tukey test for multiple comparisons. This interpretation of the interaction

Table 5
PIQ--Means and Standard Deviations for the ANOVA Group by Gender

| | | Females | Males | Group Main Effect |
|---|---|---|---|---|
| A/I (Group1) | M (SD) | 70.57 (11.99) | 65.83 (14.81) | 67.37 (13.99) |
| | n | 14 | 29 | 43 |
| No-A/I (Group2) | M (SD) | 71.44 (14.91) | 78.55 (17.61) | 76.48 (16.94) |
| | n | 9 | 22 | 31 |
| Gender Main Effect | M (SD) | 70.91 (12.88) | 71.31 (17.13) | |
| | n | 23 | 51 | |

Note. A/I = Allergy/Intolerance.

df = 1,70.

indicated no significant difference between males and females for either the allergy/intolerance group or the no-allergy/intolerance group. Similarly, females in the no-allergy/intolerance group did not differ significantly from females in the allergy/intolerance group. Males, however, once again differed significantly ($p<0.01$) in the two groups. Males in the no-allergy/intolerance group (VIQ = 77.23) scored significantly higher than males in the allergy/intolerance group (VIQ = 65.59). The means for this analysis of variance for Verbal IQ (main effects and interaction) are presented in Table 6.

Research Question 2

The final chi square analysis involved comparing the observed incidence rate of milk allergy/intolerance in the participant population with the expected incidence rate based on current incidence rates in the general infant population (2-5%, Host, 1994). The 5% incidence as the expected value was used in order to provide a more conservative test of the research question. With 58% of the participant population reporting a history of milk allergy/intolerance in infancy, findings were not only significant at the 0.05 level, findings were quite robust, $X$-square(1,N=74) = 439.40,$p<0.005$. Thus, those children referred for psychological evaluation evidenced a significantly higher incidence rate of milk

allergy/intolerance than found in the general population.

Table 6
VIQ--Means and Standard Deviations for the ANOVA Group by Gender

| | | Females | Males | Group Main Effect |
|---|---|---|---|---|
| A/I (Group1) | M (SD) n | 71.79 (14.18) 14 | 65.59 (13.30) 29 | 67.60 (13.74) 43 |
| N0-A/I (Group2) | M (SD) n | 72.89 (19.09) 9 | 77.23 (15.44) 22 | 75.97 (16.38) 31 |
| Gender Main Effect | M (SD) n | 69.00 (15.87) 23 | 68.22 (15.27) 51 | |

Note. A/I = Allergy/Intolerance.

df = 1,70.

Research Question 3

A series of discriminant analyses was used to address the question of Wechsler Scale subtests as predictors of milk allergy/intolerance. Discriminant analysis (discriminant function analysis) is a form of multiple regression analysis. In discriminant analysis the predictor variables are continuous in nature, and the criterion variable is categorical. The predictor variables are regressed on the criterion variable to determine the relative contributions of those predictors. Relationships among the constituent variables may be understood through various results, including simple correlations, parameter estimates, R-square values, and hit rates. The parameter estimates (beta weights) may be used to construct a predictive equation for application to new cases. The R-square values (proportions of variance accounted for) are used to indicate the strength of contribution of a single predictor variable or any combination of predictor variables to prediction of the criterion variable (existing cases). The hit rates indicate the proportions of existing cases correctly classified into the categories of the criterion variable.

The relationship between the outcomes may be thought of as follows. The higher the correlation between a predictor variable and the criterion variable, the more that

relationship should contribute to the R-square and the hit rate. The higher the R-square (variance accounted for) the higher should be the hit rate (correct prediction). Although the predictive equation will have higher or lower predictive value depending on the original R-square and the associated parameter estimates, any new sample will yield a lower hit rate than the hit rate derived from the current sample. No particular predictable relationship exists between the R-square or hit rate of a current sample and the outcomes of prediction using the predictive equation with a new sample.

First, a discriminant analysis was computed in which the five verbal subtest (Information, Similarities, Arithmetic, Vocabulary, and Comprehension) scaled scores were the predictor variables, and group (no milk allergy/intolerance versus milk allergy/intolerance) was the criterion variable. Results of the analysis appear in Table 7. In that table, it may be noted, Arithmetic and Comprehension were negatively correlated with the criterion variable of milk allergy/intolerance (coded 1) versus no milk allergy/intolerance (coded 0) (both $p<0.01$). Additionally, Vocabulary was negatively correlated with the criterion variable ($p<0.05$). Information and Similarities were not correlated with the criterion variable ($p>0.05$). The proportion of variance accounted for by these five variables was 22.3% (R-square = 0.223). The hit rate from this discriminant analysis was 72.1%. In Table 7, it may be noted, better prediction was achieved for participants who

were in the milk allergy/intolerance group (31/40 = 77.5%) than in the no milk allergy/intolerance group (18/28 =

Table 7

Discriminant Analysis and Predictive Equation based on Verbal IQ Subtests

1. Verbal Subtest | Correlation with A/I(1) versus No A/I(0) | p<

| | | |
|---|---|---|
| Information | -0.11 | * |
| Similarities | -0.13 | * |
| Arithmetic | -0.35 | 0.01 |
| Vocabulary | -0.20 | 0.05 |
| Comprehension | -0.30 | 0.01 |

2. R-square = 0.223 = 22.3%

3. Hit Rate = 49/68 = 0.721 = 72.1%

| | Into 0 | Into 1 |
|---|---|---|
| From 0 | 18 | 10 |
| From 1 | 9 | 31 |

4. Predictive Equation

Predicted A/I =

0.83 + (0.07 x Information) + (0.04 x Similarities) + (-0.08 x Arithmetic) + (-0.03 x Vocabulary) + (-0.05 x Comprehension)

Note. A/I = Allergy/Intolerance.

No A/I = 0. A/I = 1.

*p > 0.05.

64.3%). Parameter estimates (beta weights) are reported in the predictive equation. In such a model, the first term is the constant, or intercept. Thereafter, the parameter estimates derived from the present participants would be multiplied by the subtest scores of a future individual. If the predicted milk allergy/intolerance value from this equation is less than 0.50, then the individual is more likely to have no history of milk allergy intolerance in infancy. In contrast, if the predicted milk allergy/intolerance value from this equation is greater than 0.50, then the individual is more likely to have a history of milk allergy/intolerance in infancy.

Second, a discriminant analysis was computed in which the five performance subtest (Picture Completion, Coding, Picture Arrangement, Block Design, and Object Assembly) scaled scores were the predictor variables, and group (no milk allergy/intolerance versus milk allergy/intolerance) was the criterion variable. Results of the analysis appear in Table 8. In that table, it may be noted, Picture Arrangement was negatively correlated with the criterion variable of milk allergy/intolerance (coded 1) versus no milk allergy/intolerance (coded 0) ($p<0.01$). Picture Completion, Coding, Block Design, and Object Assembly were also negatively correlated with the criterion variable (each

p<0.05). The proportion of variance accounted for by these 5 variables was 21.9% (R-square = 0.219). The hit rate from this discriminant analysis was 70.8%. In Table 8, it may be

Table 8

Discriminant Analysis and Predictive Equation based on Performance IQ Subtests

| 1. Performance Subtest | Correlation with A/I(1) versus No A/I(0) | p< |
|---|---|---|
| Picture Completion | -0.31 | 0.01 |
| Coding | -0.38 | 0.05 |
| Picture Arrangement | -0.32 | 0.05 |
| Block Design | -0.38 | 0.05 |
| Object Assembly | -0.24 | 0.05 |

2. R-square = 0.219 = 21.9%

3. Hit Rate = 34/48 = 0.708 = 70.8%

| | Into 0 | Into 1 |
|---|---|---|
| From 0 | 12 | 8 |
| From 1 | 6 | 22 |

4. Predictive Equation

Predicted A/I =

0.97 + (-0.03 x Picture Completion) + (-0.02 x Coding)
+ (-0.01 x Picture Arrangement)
+ (-0.04 x Block Design) + (-0.05 x Object Assembly)

---

Note. A/I = Allergy/Intolerance.

No A/I = 0. A/I = 1.

noted better prediction was achieved for participants who were in the milk allergy/intolerance group (22/28 = 78.6%) than in the no milk allergy/intolerance group (12/20 = 60.0%). Parameter estimates (beta weights) are reported in the predictive equation. As noted previously, the first term is the constant, or intercept. Thereafter, the parameter estimates derived from the present participants would be multiplied by the subtest scores of a future individual. If the predicted milk allergy/intolerance value from this equation is less than 0.50, then the individual is more likely to have no history of milk allergy intolerance in infancy. In contrast, if the predicted milk allergy/intolerance value from this equation is greater than 0.50, then the individual is more likely to have a history of milk allergy intolerance in infancy.

Third, a discriminant analysis was computed in which the two subtests (Arithmetic and Coding) displaying the greatest between group differences (>2 points) in mean scaled scores were the predictor variables, and group (no milk allergy/intolerance versus milk allergy/intolerance) was the criterion variable. Results of the analysis appear in Table 9. In that table, it may be noted Arithmetic was negatively correlated with the criterion variable of milk

allergy/intolerance (coded 1) versus no milk allergy/intolerance (coded 0) ($p<0.01$). Coding was also negatively correlated with the criterion variable ($p<0.05$). The proportion of variance accounted for by these 2

Table 9

Discriminant Analysis and Predictive Equation based on Arithmetic and Coding Subtests

1. Subtest

| Subtest | Correlation with A/I(1) versus No A/I(0) | p< |
|---|---|---|
| Arithmetic | -0.43 | 0.01 |
| Coding | -0.30 | 0.05 |

2. R-square = 0.191 = 19.1%

3. Hit Rate = 39/53 = 0.736 = 73.6%

| | Into 0 | Into 1 |
|---|---|---|
| From 0 | 11 | 10 |
| From 1 | 4 | 28 |

4. Predictive Equation

Predicted A/I =

0.94 + (-0.06 x Arithmetic) + (-0.01 x Coding)

Note. A/I = Allergy/Intolerance.

No A/I = 0. A/I = 1.

variables was 19.1% (R-square = 0.191). The hit rate from this discriminant analysis was 73.6%. In Table 9, it may be noted better prediction was achieved for participants who were in the milk allergy/intolerance group (28/32 = 87.5%) than in the no milk allergy/intolerance group (11/21 = 52.4%). Parameter estimates (beta weights) are reported in the predictive equation. The first term is the constant, or intercept. Thereafter, the parameter estimates derived from the present participants would be multiplied by the subtest scores of a future individual. If the predicted milk allergy/intolerance value from this equation is less than 0.50, then the individual is more likely to have no history of milk allergy intolerance in infancy. In contrast, if the predicted milk allergy/intolerance value from this equation is greater than 0.50, then the individual is more likely to have a history of milk allergy intolerance in infancy.

Fourth, a discriminant analysis was computed in which the Perceptual Organization Index and Verbal Comprehension Index were the predictor variables, and group (no milk allergy/intolerance versus milk allergy/intolerance) was the criterion variable. Results of the analysis appear in Table 10. In that table, it may be noted Perceptual Organization was negatively correlated with the criterion variable of

milk allergy/intolerance (coded 1) versus no milk allergy/intolerance (coded 0) ($p<0.01$). Verbal Comprehension was not significantly correlated with the criterion variable ($p>0.05$). The proportion of variance accounted for by these

Table 10

Discriminant Analysis and Predictive Equation based on Perceptual Organization and Verbal Comprehension Indexes

| 1. Index | Correlation with A/I(1) versus No A/I(0) | p< |
|---|---|---|
| Perceptual Organization | -0.43 | 0.01 |
| Verbal Comprehension | -0.30 | * |

2. R-square = 0.102 = 10.2%

3. Hit Rate = 35/53 = 0.660 = 66.0%

| | Into 0 | Into 1 |
|---|---|---|
| From 0 | 12 | 11 |
| From 1 | 7 | 23 |

4. Predictive Equation

Predicted A/I =

1.38 + (-0.008 x Perceptual Organization)

+ (-0.004 x Verbal Comprehension)

Note. A/I = Allergy/Intolerance.

No A/I = 0. A/I = 1.

* $p$ > 0.05.

2 variables was 10.2% (R-square = 0.102). The hit rate from this discriminant analysis was 66.0%. In Table 10, it may be noted better prediction was achieved for participants who were in the milk allergy/intolerance group (23/30 = 76.7%) than in the no milk allergy/intolerance group (12/23 = 52.2%). Parameter estimates (beta weights) are reported in the predictive equation. The first term is the constant, or intercept. Thereafter, the parameter estimates derived from the present participants would be multiplied by the Index scores of a future individual. If the predicted milk allergy/intolerance value from this equation is less than 0.50, then the individual is more likely to have no history of milk allergy intolerance in infancy. In contrast, if the predicted milk allergy/intolerance value from this equation is greater than 0.50, then the individual is more likely to have a history of milk allergy intolerance in infancy.

Owing to the fact that the current study involved three separate research questions, and findings were represented in no less than ten separate tables, a brief summary of the current findings is provided. This summary may be seen in Table 11.

Table 11

Summary of Current Findings

1. Milk A/I related to:
   - Lower mean IQ scores
   - Below average, or lower, IQ
   - Borderline, or lower, IQ
   - Referral for Psychological Evaluation

2. Wechsler Intelligence Scales Good Predictors of Milk A/I:

| | |
|---|---|
| Performance Subtests hit-rate | 70.8% |
| Verbal Subtests hit-rate | 72.1% |
| Arithmetic and Coding hit-rate | 73.6% |
| Perceptual Organization and Verbal Comprehension hit-rate | 66.0% |

3. Gender Factor
   - Males with Milk A/I 12.97 point disadvantage, compared to No Milk A/I males, on Full Scale IQ scores. Similar findings on both Verbal and Performance IQ scores.
   - Females with Milk A/I 0.92 point disadvantage, compared

to No Milk A/I females, on Full Scale IQ scores. Similar findings on both Verbal and Performance IQ scores.

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Note. A/I = Allergy/Intolerance.

## Chapter 4

## Discussion

The results of this study underscore the likelihood that dietary factors, specifically allergy or intolerance to milk proteins, are highly relevant to cognitive functioning. The findings support the hypothesized relationship between a reported history of cow's milk allergy/intolerance in infancy and below average cognitive functioning in later childhood. Children with history of milk allergy/intolerance more frequently demonstrated IQ scores at or below the below-average range of intelligence when compared with children with no history of milk allergy/intolerance. Additionally, children with a history of milk allergy/intolerance more frequently demonstrated IQ scores at or below the borderline range of intelligence than did their no history of milk allergy/intolerance counterparts. Furthermore, children with a history of milk allergy/intolerance demonstrated significantly lower mean IQ scores on objective measures of intelligence, as opposed to children with no such history.

Further substantiated by the results is the conclusion that children referred for psychological evaluation report a

higher incidence rate of milk allergy/intolerance in infancy than reported in the general infant population. With 58% of the 74 participants reporting a history of milk allergy/intolerance, as opposed to the expected 5% for a general population, the relationship between milk allergy/intolerance and being referred for a psychological evaluation is highly plausible.

The discriminant analyses revealed the Wechsler Scale subtests as useful predictors of milk allergy/intolerance. The Performance Scales yielded a hit-rate of 70.8%. Verbal Scales yielded a hit-rate of 72.1%. Perceptual Organization Index and Verbal Comprehension Index together yielded a hit-rate of 66.0%. Combining subtests Arithmetic and Coding, selected as predictor variables by virtue of their displaying the greatest between-group differences (>2 points) in mean scaled scores, proved the best indicator with a hit-rate of 73.6%. These two subtests, Arithmetic and Coding, are purported measures of attention, freedom from distractibility, numerical ability, and short term memory (Sattler, 1992). Both are undoubtedly measures of concentration, and both may be related to information-processing strategies. Most certainly, the two subtests require cognitive flexibility or the ability to make a mental shift. As one might anticipate, the two-plus point advantage in mean score went to Group Two (no milk allergy/intolerance) on each of the two subtests, Arithmetic and Coding.

Disorders that frequently display difficulties in cognitive flexibility and mental shift, such as autism and obsessive-compulsive disorder (American Psychiatric Association, 1994; Meyer, 1993), appear to be affected, at least in some cases, by vitamin B6. Although we are unsure of the mechanisms involved in the efficacy of B6 treatment in children with autism, we do know that B6 most likely has an effect in the treatment of obsessive-compulsive disorder (OCD) because it is necessary in the synthesis of serotonin (Sierles, 1993). Drugs that inhibit the reuptake of serotonin play an important role in the treatment of OCD as well as in the treatment of depression, a frequent co-diagnosis of OCD (Carlson, 1998). Serotonin has long been associated with depression (Sierles, 1993). Of further interest, diminished ability to concentrate is one diagnostic criterion for major depression (American Psychiatric Association, 1994). If there is indeed a common factor in the etiology of the above mentioned disorders, then research designed to disentangle the relationship(s) between them could prove useful in terms of future treatment.

Even more provocative, perhaps, is the apparent connection between a history of milk allergy/intolerance and impairments in verbal skills. In Analysis One, Group One (milk/allergy intolerance) and Group Two (no milk allergy/intolerance) demonstrated greater disparity on the Verbal IQ scores as opposed to the Performance IQ scores in

the average versus below average range of intelligence. A similar pattern was revealed in Analysis Two, wherein scores indicative of borderline intellectual functioning were used as the cut-off criterion. Again, the connection between milk allergy/intolerance and impairments in verbal skills was demonstrated by the greater disparity between Group One and Group Two on the Verbal IQ scores as opposed to the Performance IQ scores. This is not surprising in view of suggestions in the literature (Lucarelli et al., 1995; Moreno et al., 1992; Reichelt, Knivsberg, Lind, & Nodland, 1991) that the processing of proteins and amino acids is connected not only to intelligence in general, but also to verbal skills specifically.

In considering the processing of proteins, which may be an underlying factor in the impaired functioning displayed by participants, one may further consider genetic factors as they relate to such processes. Not only is mental retardation observed more frequently in males, but various language disorders such as Expressive Language disorder, Mixed Receptive-Expressive Language disorder, Phonological disorder, Stuttering, and Autism (with its delay in, or total lack of, spoken language development) all evidence a higher incidence rate in males (American Psychiatric Association, 1994). Such gender skew is commonly viewed by scientists as being indicative of underlying genetic factors. Results of the current study strongly suggest gender as a determinant in the relationship between milk

allergy/intolerance and impaired cognitive functioning. While females with no history of milk allergy/intolerance demonstrated only a 0.92 point advantage over their milk allergic/intolerant counterparts on Full Scale IQ scores, males with no history of milk allergy/intolerance demonstrated a generous advantage of 12.97 points over their milk allergic/intolerant compeers on Full Scale IQ scores. The findings were similar for both Verbal and Performance IQ scores, with non-milk allergic/intolerant males demonstrating a distinct advantage (11.64 points and 12.72 points, respectively) over milk allergic/intolerant males. Females with no milk allergy/intolerance showed only a slight advantage on each of the two IQ scales (1.1 points Verbal and 0.87 points Performance) when compared to females with a history of milk allergy/intolerance.

Again, gender skew is commonly viewed by scientists as being indicative of underlying genetic factors. The X chromosome is frequently associated with disorders having a higher incidence rate in males since males have only one X chromosome as opposed to females, who have two X chromosomes. Having two X chromosomes allows for the possibility of one undamaged X chromosome "making up" for damage to its counterpart. Since the results of the current study implicate gender as a determining factor in the relationship between milk allergy/intolerance and cognitive functioning, one might also speculate regarding the nature of the relationship between genetic factors, such as the X

chromosome, and verbal skills, inasmuch as the results also suggest a greater impact of milk allergy/intolerance on verbal skills as opposed to performance skills.

Chromosomes consist of long strands of deoxyribonucleic acid (DNA). The chromosomes do not directly perform any tasks, but they have an important function; they contain the recipes for making proteins, as well as the recipes for breaking them down. Sections of the chromosomes, genes, contain the recipes for individual proteins. When a particular protein is needed, a copy is made of the recipe contained in a specific gene. This copy travels out of the nucleus into the cytoplasm, where the protein is assembled from its constituents, amino acids. Similarly, amino acids are obtained from proteins. Such reactions are catalyzed by specific enzymes. Protein structure and enzyme structure are determined by genetic code.

Though the role of enzymes and bacteria in specific disorders is most certainly beyond the scope of this report, it may yet be germane to consider their implication. As enzyme structure is also controlled by genetic code, possibly an individual might inherit a predisposition for abnormal enzyme production. It is also relevant to note, as previously mentioned, some antibiotics can block enzyme activity. Though not a focus of the current study, it is interesting at this point to consider that since many children (57%) in this study also reported a history of chronic ear infection (CEI), with subsequent antibiotic

treatment, it is possible such treatment with antibiotics may have, at least in some instances, exacerbated already existing problems of enzyme functioning. Information included in the participants' casefolders showed that while 42% of Group Two participants reported a history of CEI, 67% of Group One participants reported CEI history. The history of CEI and accompanying antibiotic treatment alone would not appear to wholly explain the occurrence of below average cognitive functioning since among children in Group Two, of those with average or better IQs across the three scales--Full, Verbal, and Performance--75% reported a history of CEI. Of further relevance, "allergy of infection," or cell-mediated allergy, is frequently encountered following infection by certain bacteria, viruses, or fungi (Frobisher et al., 1974).

Of course, enzymes act as part of a well organized system. And what affects one portion of the system will affect other parts of the system as well. Thus, there are many ways in which enzymes can be "controlled," inhibited, or repressed. Given the complexity of such a system, a thorough understanding is no simple matter. As a venue of study, the relationship of enzyme functioning to bacterial, viral, fungal and/or genetic influences as they together affect cognitive functioning and verbal skills, seems even more abstruse than the concept's verbal presentation. It might involve a lifetime, several lifetimes, of intense investigation. Although, among the current study's findings

is a correlation between milk allergy/intolerance in infancy and cognitive functioning and verbal skills in later childhood, causality cannot be stated. A statement of causality was not the purpose of this study. Again, enzyme functioning and bacterial influences as underlying factors merit further consideration. Moreover, the possibility of various proteins (and other non-protein nutrients as well) playing a significant, if not profound, role in cognitive functioning deserves further attention.

In terms of future research, it might be important to compare children age three years through twelve years identified by physician report as having a history of milk/allergy intolerance in infancy and subsequently returned to milk products, with same-age children who have had no indications of milk/allergy intolerance in infancy. Comparing objective measures of language development, verbal skills, perceptual organization, and cognitive functioning between the two groups, as well as between genders, might further discern the relationship between milk allergy/intolerance and cognitive functioning as demonstrated by the current study.

Complete certainty regarding the allergic history of the participants may be considered a major limitation of the current study since participant histories were provided by primary caregiver report. In consideration of this stated limitation, two observations are relevant. First, even though the mean IQ scores of Group One (history of milk

allergy/intolerance) participants were significantly lower than the mean IQ scores of Group Two (no history of milk allergy/intolerance) participants, the IQ scores of both Group One and Group Two were generally below average. Second, among those children reporting no history of milk allergy/intolerance (Group Two), many, if not most, displayed indications of allergy (e.g. red ears, red cheeks, and chronic congestion). Most Group One participants also displayed such indications. Of further relevance, and as previously stated, those children who reported a history of milk/allergy intolerance in infancy(Group One) had been returned to diets containing milk products. Although the information regarding indications of allergy/intolerance was not formally included as a part of this study, the observations were typically included in the individual's case folder under "Mental Status Examination: Appearance." The observed indications of allergy/intolerance may be relevant when considering the possibility that some Group Two participants had undiagnosed allergies. Thorough allergy testing might have been helpful. Most likely, some Group Two participants would have been identified as milk allergic/intolerant. Equally likely is the possibility some Group One participants might have been categorized by such testing as having no milk allergy/intolerance. The latter possibility is accentuated by the suggestion that only one-third of all allergic reactions are histamine-mediated (immunologic), the remaining two-thirds being kinin-mediated

(non-immunologic) (Philpott & Kalita, 1980). If this is so, then many children, both in the participant population and in the general population, who are indeed having allergic reactions would go undiagnosed by standard (immunological) allergy tests. This might explain in part the better prediction achieved for participants in the milk allergy/intolerance group, as opposed to participants in the no milk allergy/intolerance group by each of the three discriminant analyses. It is suggested, participants reporting a history of milk allergy/intolerance in infancy were more accurately represented regarding milk allergy/intolerance status than were participants reporting no such history.

Even so, the term allergy/intolerance may be interpreted more precisely by some readers of this report than by others. The author does not intend an overly strict designation by the term. The author conceptualizes the term to mean an underlying difficulty in processing some constituent of the milk product. For some individuals, this difficulty may be revealed by standard allergy testing. For other individuals, a more common-sense, if less than scientific, approach may reveal the difficulty (such as a cessation or lessening of symptoms following discontinued ingestion of the implicated food item).

For now, without understanding the mechanisms underlying the correlation between milk allergy/intolerance and cognitive functioning and verbal skills, perhaps the

best we can do is heighten awareness of the relationship and be cautious in treating those children with indications of allergy/intolerance. In terms of being cautious, frankly refusing to dismiss indications of allergy/intolerance, realizing that allergy tests are not always definitive, and taking time to ask for--and listen to--parent report are an important beginning. Furthermore, avoidance of implicated food items specific to the child, seems only sensible. Knowing "why" is helpful, not essential. Knowing "that" is a start, not an end.

Summary

As reviewed in Table 1, recent research underscores the important role of dietary factors in level of cognitive functioning. Recent research suggests a relationship between allergy/intolerance to specific food elements and verbal skills, problem behavior, and level of cognitive functioning (Lucarelli et al., 1995; Moreno et al., 1992; Reichelt, Knivsberg, Lind, & Nodland, 1991). Research further suggests benefits to cognitive functioning for children fed breast milk as opposed to formula (Florey et al., 1995; Johnson et al., 1996; Morley et al., 1988). With the differences in cognitive development and the heightened negative reactions in children who demonstrate milk allergy/intolerance, might such milk allergic/intolerant children display an even greater degree of impact on intelligence?

The current study examined the relation between a reported history of milk allergy/intolerance in infancy and

level of cognitive functioning in later childhood. Findings were significant for a relationship between history of milk allergy/intolerance and level of cognitive functioning, with milk allergy/intolerance children demonstrating lower mean IQ scores compared to children with no history of milk allergy/intolerance. A connection between verbal skills and milk allergy/intolerance was also suggested. A greater disparity was evidenced between milk allergic/intolerant children versus no milk allergy/intolerance children on Verbal IQ scores, as opposed to Performance IQ scores at both the below average and borderline intelligence levels. Gender is suggested as a determining factor since males with allergy/intolerance showed a significant disadvantage in mean IQ scores when compared with males with no allergy/intolerance. Females with milk allergy/intolerance showed no significant disadvantage when compared with their no milk allergy/intolerance counterparts. This should not be too surprising in light of the fact that mental retardation and various language disorders are observed more frequently in males (American Psychiatric Association, 1994). This again underscores the importance of genetics, possibly the x chromosome, as a factor in intelligence in general, and in verbal skills specifically.

The current study found Wechsler intelligence scale subtests to be good predictors of milk allergy/intolerance. Performance IQ subtests produced a hit-rate of 70.8%. Verbal IQ subtests produced a hit-rate of 72.1%. Arithmetic and

Coding produced a hit-rate of 73.6%. Furthermore, the current study found a significant correlation between a history of milk allergy/intolerance in infancy and being referred for psychological evaluation in later childhood.

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